Sequential and SequentialDesign: Tools For Prospective Sequential Medical Product Safety Surveillance

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ICPE Disclosures

- Funding sources:
  - National Institute of General Medical Sciences, National Institutes of Health (NIH), USA, R01GM108999
  - U.S. Food and Drug Administration, FDA HHSF223201400030I, Task Order: HHSF22301003T

- No relationships to disclose
- The views expressed are the authors' and not necessarily those of the Food and Drug Administration, or the Department of Health and Human Services

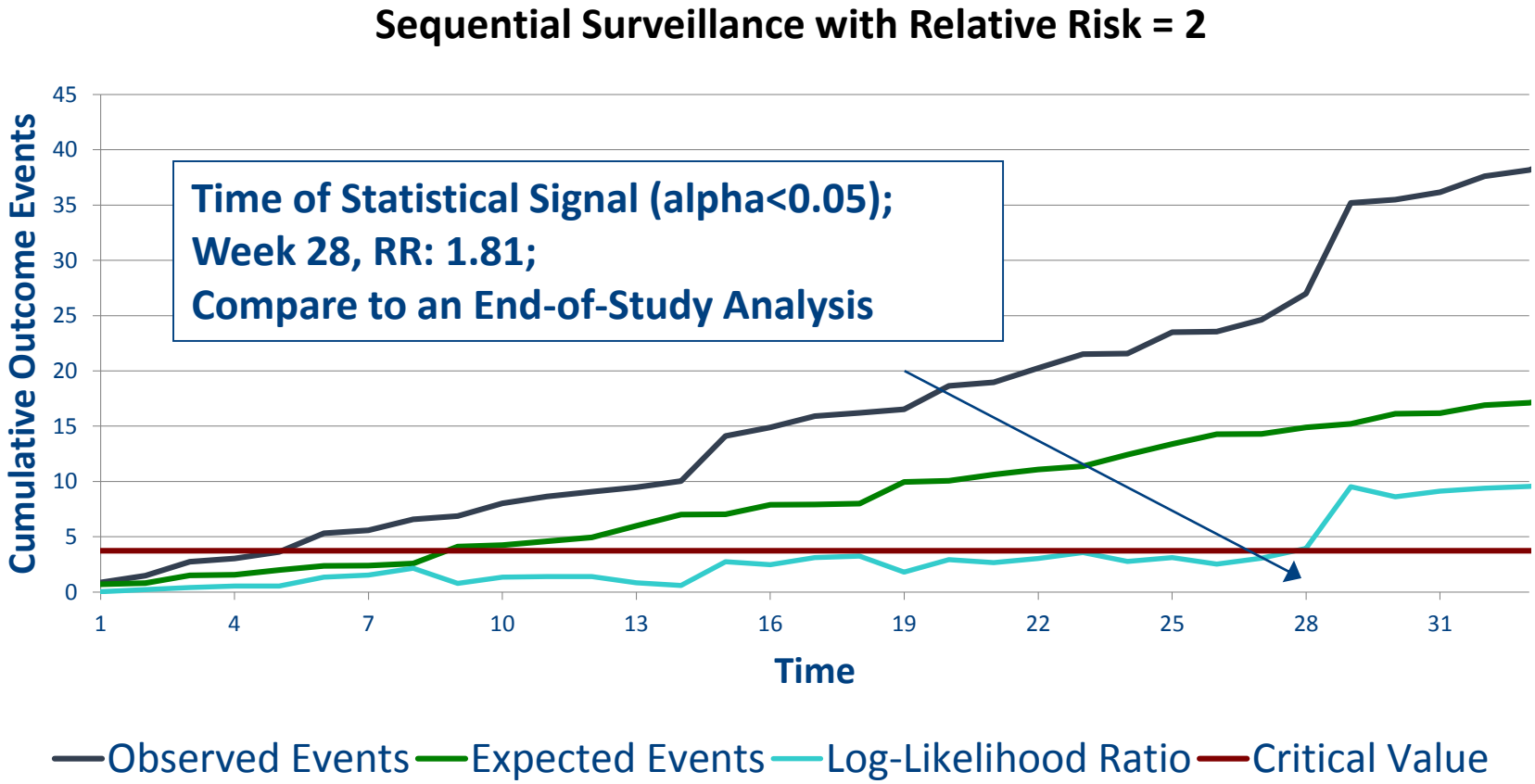
Agenda

- Overview of Sequential Surveillance Theory
- Vaccine Safety Surveillance
- Drug Safety Surveillance
- Interactive Demonstration of Sequential Software
- Q&A

Overview of Sequential Surveillance Theory

Bruce Fireman

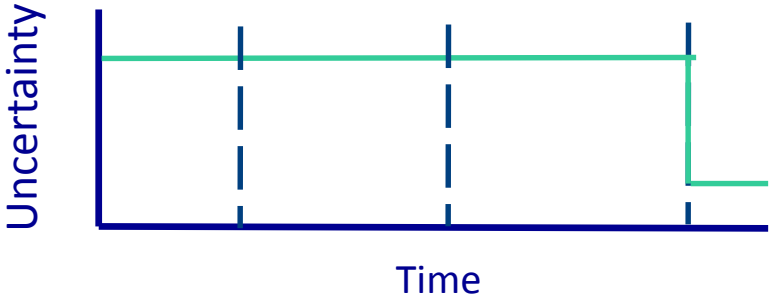
Sequential v. Non-Sequential Surveillance



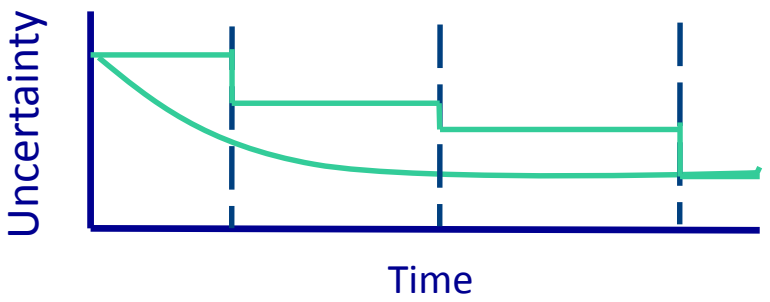
Why Sequential Surveillance?

- Opportunities to detect elevated risk sooner
- However, one has to monitor for longer periods of time (i.e., accrue more events) to achieve the same statistical power at end-of-study.

Traditional Epidemiological Study Design:



Sequential Surveillance Study Design:



Sequential Statistical Analysis Born in Clinical Trials

	Clinical Trials	Observational Data
Data Characteristics	Primary use data collected for research	Secondary use data collected for healthcare
Sample Size	Add 1 Patient at a Time	Add 1 Database at a Time
Optimal Performance	Minimize interim hypothesis tests to minimize time to reach end-of-study with desired power	Maximize ability to detect a signal (i.e., test often) and continue monitoring to achieve same power

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Sequential Analysis

ISSN: 0747-4946 (Print) 1532-4176 (Online) Journal homepage: http://www.tandfonline.com/loi/lsqa20

A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance

Martin Kulldorff , Robert L. Davis , Margarette Kolczak† , Edwin Lewis , Tracy Lieu & Richard Platt

- MaxSPRT builds off Wald's Sequential Probability Ratio Test (SPRT) but creates a composite alternative hypothesis
- Uses exact statistics instead of asymptotic theory or normal approximations
- Supports Poisson type data or Binomial data

Early Sequential Surveillance in the Vaccine Safety Datalink

ORIGINAL ARTICLE

Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,‡ Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,* Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team*

Early Sequential Surveillance in the Vaccine Safety Datalink

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Real-Time Vaccine Safety Surveillance for the Early Detecti

Tracy A. Lieu, MD, MPH,†*
Edwin M. Lewis, MPH,§ Eric Wei
Jeffrey S. Brown, PhD, and Richard*

PEDIATRICS®
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Active Surveillance for Adverse Events: The Experience of the Vaccine Safety Datalink Project

W. Katherine Yih, Martin Kulldorff, Bruce H. Fireman, Irene M. Shui, Edwin M. Lewis, Nicola P. Klein, James Baggs, Eric S. Weintraub, Edward A. Belongia, Allison Naleway, Julianne Gee, Richard Platt and Tracy A. Lieu

Pediatrics published online Apr 18, 2011;
DOI: 10.1542/peds.2010-1722I

Methodological Improvements I

- Expansion from strictly continuous to hybrid continuous/group sequential hypothesis testing approaches
  - Eliminated “alpha wasting” (and consequent losses in power) when unspent but allocated alpha accrued
  - Silva IR, Kulldorff M. (2015), Continuous versus Group Sequential Analysis for Vaccine and Drug Safety Surveillance. Biometrics, 71 (3), 851–858
- Creation of minimum threshold for hypothesis testing to prevent early signaling
  - Kulldorff M, Silva IR. (2015). Continuous Post-market Sequential Safety Surveillance with Minimum Events to Signal. REVSTAT Statistical Journal, 15(3): 373–394.

Published in final edited form as:
Biometrics. 2015 September ; 71(3): 851–858. doi:10.1111/biom.12324.

Continuous Versus Group Sequential Analysis for Post-Market Drug and Vaccine Safety Surveillance

I. R. Silva[1,2,*] and **M. Kulldorff**[1]

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[2]Department of Statistics, Federal University of Ouro Preto, Ouro Preto, Minas Gerais, Brazil

- There is always a continuous design with shorter expected time-to-signal than the best group sequential design.
- Recommendation: Perform hypothesis tests on data as they arrive in whatever batches they arrive in.

Methodological Improvements II

- Optimal alpha spending to minimize expected time-to-signal
  - Assumes a concave down shape

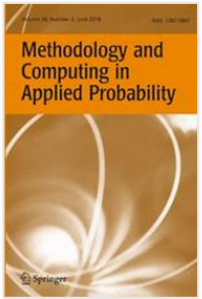
Statistics
in Medicine

RESEARCH ARTICLE | Free Access

Type I error probability spending for post–market drug and vaccine safety surveillance with binomial data

Ivair R. Silva

First published: 25 September 2017 | https://doi.org/10.1002/sim.7504



Methodology and Computing in Applied Probability
June 2018, Volume 20, Issue 2, pp 739–750 | Cite as

Type I Error Probability Spending for Post-Market Drug and Vaccine Safety Surveillance With Poisson Data

Authors | Authors and affiliations

Methodological Improvements III

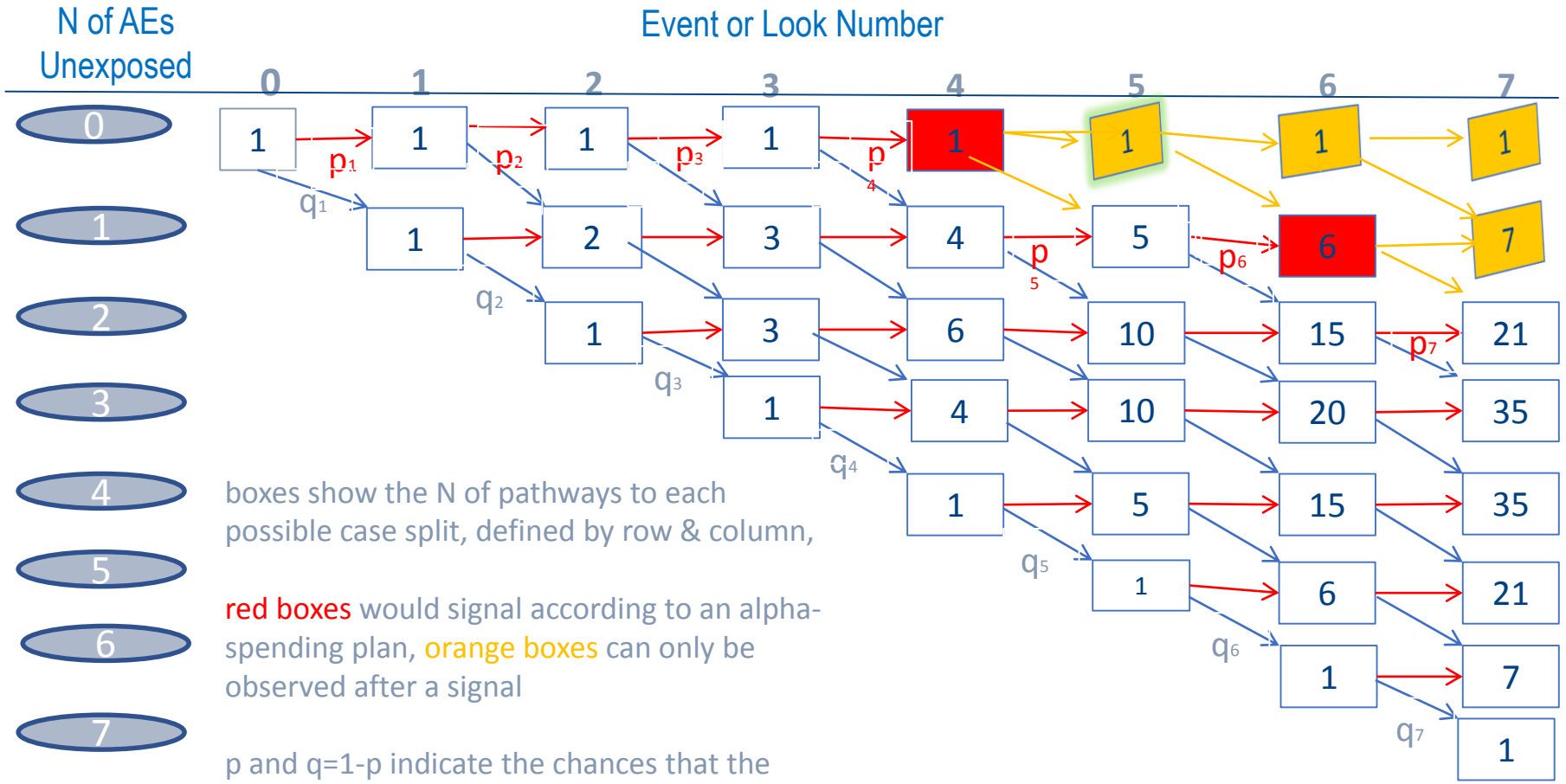
$$LR_n = \max_{H_A} \frac{P(C_n = c_n|H_A)}{P(C_n = c_n|H_0)} = \max_{RR>1} \frac{[RR/(z+RR)]^{c_n}[z/(z+RR)]^{n-c_n}}{[1/(z+1)]^{c_n}[z/(z+1)]^{n-c_n}}$$

The maximum likelihood estimate of RR is $zc_n/(n-c_n)$. So

$$LR_n = \frac{(c_n/n)^{c_n}[(n-c_n)/n]^{n-c_n}}{[1/(z+1)]^{c_n}[z/(z+1)]^{n-c_n}}$$

- We need a matrix of information: (z/p, treatment cases, comparator cases).
- z/p represents the probability of a case being in the treatment group under the null hypothesis.
- Key Innovation: let z be a vector not a scalar!

Diagram of the first 7 Looks in a Continuous Sequential Analysis



boxes show the N of pathways to each possible case split, defined by row & column,

red boxes would signal according to an alpha-spending plan, orange boxes can only be observed after a signal

p and q=1-p indicate the chances that the next event will exposed or unexposed

American Journal of Epidemiology

Vol. 170, No. 5
DOI: 10.1093/aje/kwp173
Advance Access publication July 22, 2009

Practice of Epidemiology

Influenza Vaccination and Mortality: Differentiating Vaccine Effects From Bias

Bruce Fireman, Janelle Lee, Ned Lewis, Oliver Bembom, Mark van der Laan, and Roger Baxter

Initially submitted February 6, 2009; accepted for publication June 2, 2009.

- Appendix proof shows a case-centered logistic regression is mathematically equivalent to a stratified Cox proportional hazards model.
- Key innovation: Treat "survival" data as binary / Binomial data.

Summary

- Methodological advances to adapt sequential statistical analysis from the context of clinical trials to the context of observational database studies continue:
  - Adaptation for the manner in which data arrive.
  - Adaptation to cover commonly employed study designs (e.g., propensity score matched analysis with variable matching).
  - Continued optimization to minimize expected time-to-signal (i.e., detect a risk as soon as possible).

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34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink

Andreia Leite

Public Health England

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Vaccine 35 (2017) 6885–6892

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD)

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ARTICLE INFO

Article history:
Received 22 May 2017
Received in revised form 4 September 2017
Accepted 6 September 2017
Available online 19 October 2017

Keywords:
Electronic health records
Safety
Surveillance
Timeliness
Vaccines

ABSTRACT

Introduction: Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is increasingly used to rapidly detect vaccine safety signals. NRTVSS has not been fully implemented in the UK. We assessed the feasibility of implementing this surveillance using the UK Clinical Practice Research Datalink (CPRD).

Methods: We selected seasonal influenza vaccine/Guillain-Barré Syndrome (GBS) as an example of a rare outcome and measles–mumps–rubella (MMR) vaccine/febrile seizures as a positive control. For influenza/GBS we implemented a system for the 2013/2014 and 2014/2015 influenza seasons; for MMR/seizures the surveillance period was July 2014–June 2015. We used the continuous Poisson-based maximized sequential probability ratio test (PMaxSPRT), comparing observed-to-expected events, for both pairs. We calculated an age-sex-adjusted rate using 5 years of historic data and used this rate to calculate the expected number of events in pre-specified post-vaccination risk-window (GBS: 0–42 days, seizures: 6–21 days). For MMR/seizures we also implemented the system using the Binominal-based maximized sequential probability ratio test (BMaxSPRT). For this, we compared seizures in the risk-window (6–21 days) to a control window (0–5 and 22–32 days). Delays in recording outcomes influence the data available, so we adjusted the expected number of events using a historical distribution of delays in recording GBS/febrile seizures. Analyses were run using data up to each CPRD monthly release. We also performed power calculations for detecting increases in relative risk (RR) from 1.5 to 10.

Results: For influenza/GBS we implemented a system in both seasons with no signal. Power to detect a signal was >80% for RR $\geq$ 4. For MMR/seizures we were able to identify a signal with PMaxSPRT but not with BMaxSPRT. Power $\geq$ 80% for RR $\geq$ 2.5 for both tests.

Conclusion: CPRD is a potential data source to implement NRTVSS to exclude large increases in the risk of rare outcomes after seasonal influenza and lower increases in risk for more frequent outcomes.

1. Introduction

Near real-time vaccine safety surveillance (NRTVSS) using electronic health records is amongst the tools available to perform post-licensure vaccine safety surveillance. NRTVSS is usually started shortly after a new vaccine is introduced and data is analysed at repeated points in time. Near real-time surveillance was introduced in the USA in 2005 first using the sequential probability ratio test and later its maximized version. It is now used routinely in this country [1]. It has allowed the identification of several safety signals [2].

In the UK, there are electronic health records available such as the Clinical Practice Research Datalink (CPRD). NRTVSS has been implemented in the UK using spontaneous reports to obtain the observed number of events and CPRD to calculate the expected number of events. This implementation inherits spontaneous reports limitations, including underreporting [3]. A NRTVSS fully relying on electronic health records has not been implemented to date.

When envisaging a new data source to implement NRTVSS timeliness is a key consideration. In CPRD, delays can happen due to: (i) delays in making a diagnosis after an initial consultation; (ii) delays in recording diagnosis made in other levels of care (e.g. hospital); (iii) delays in receiving data for analysis. To the best

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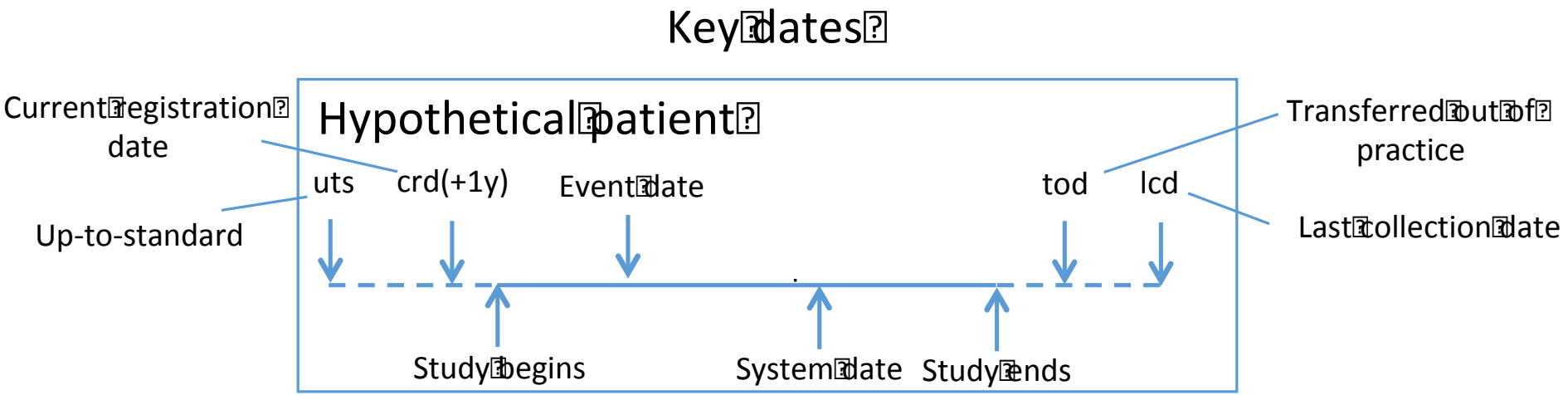
https://doi.org/10.1016/j.vaccine.2017.09.022
0264-410X/

Clinical Practice Research Datalink

- CPRD – UK primary care database:
  - 4.4 million active patients by mid-2013;
  - Information on diagnosis, vaccines administered in primary care, referrals/feedback from secondary care;
- CPRD availability and key dates
  - Data is made available monthly to researchers;
  - Practices upload their data some time before that (last collection date, lcd);

Clinical Practice Research Datalink



Trial implementations: objectives

- Assess the feasibility of implementing NRTVSS using CPRD:
  - Most appropriate statistical test to detect a signal
  - Adjustment for delays
  - Power to detect an increased risk

Trial implementation: methods

	Vaccine/outcome pairs	
Characteristic	**Seasonal influenza/GBS**	**MMR/seizures**
Purpose	Rare outcome (background rate – 0.7-4.3/100,000 PY[1])	Less rare outcome and positive control
Statistical test	PMaxSPRT	PMaxSPRT and BMaxSPRT
Study population	≥ 65 years, vaccinated	12-23m, 1st MMR dose
Study period	2013/2014 and 2014/2015	August 2014 – July 2015
Historical period (for PMaxSPRT)	2008/09-2012/13 and 2009/10-2013-14	July 2009 – June 2014
Risk-window	42 days	6-21 days
Control period (for BMaxSPRT)	-	1-5 and 22-32 days

BMaxSPRT – Binomial maximized sequential probability ratio test, GBS – Guillain-Barré syndrome, m – months, MMR – Measles-mumps-rubella vaccine, PMaxSPRT – Poission maximized sequential probability ratio test, PY – Person-years.

1 – Bryan P et al. Lancet 2010; 376: 417-8.

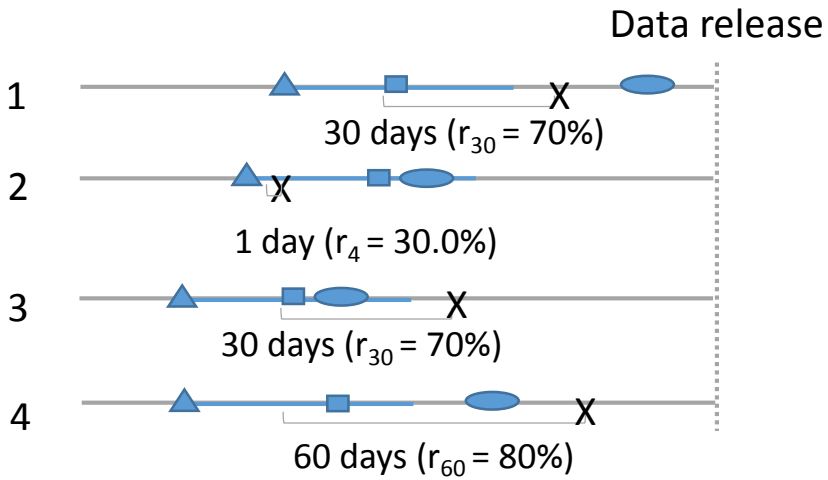
Trial implementation: adjustments

- Number of expected events (PMaxSPRT) adjusted by age and sex. GBS/seizure cases excluded if:
  - Recording delays>365 days
  - Likely to have been involved in mass transfers.

- Delays (PMaxSPRT):
  - Expected events reduced based on a previously generated delay distribution

- Delays & partially accrued periods (BMaxSPRT):
  - The ratio of the adjusted number of days in the control and risk periods was calculated and used as a matching ratio

Adjustments for data accrual (PMaxSPRT)

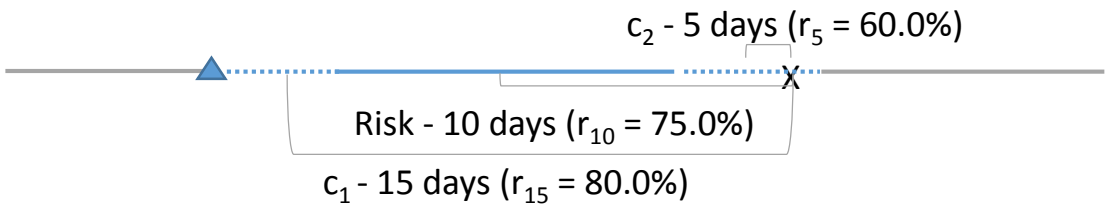


Vaccine
Event date
System date
Risk window
X Last collection date
r_d expected recording d days after the event

Average recording 62.5%

Expected recorded events in the recent data = 2.5

Adjustments for data accrual and partially accrued periods (BMaxSPRT)



	Observed	Adjusted
Period	**Period duration (days)**	
Control 1 (c_1)	5	4
Risk	15	11
Control 2 (c_2)	7	4
	Ratio (control/risk)	
Control/Risk		

Vaccine
Risk window
Control period
X Last collection date
r_d expected recording d days after the event

Power and implementation

- Power to detect a signal calculated for detecting increases in relative risk (RR) from 1.5-10;

- Implementation done graphically, by calculating the log-likelihood ratio test (LLRT) at the time of each CPRD data release (monthly):
  - PMaxSPRT – based on the number of observed and expected events
  - BMaxSPRT – based on the number of observed events in the control and risk periods.

- For influenza/GBS further implementation assuming an increase in risk that should be detected according to power calculations.

- The results from the LLRT were compared with the critical limit. For PMaxSPRT this was done requiring at least 1, 2, and 4 events before raising a signal.

- R Package *Sequential* version 2.3.1.

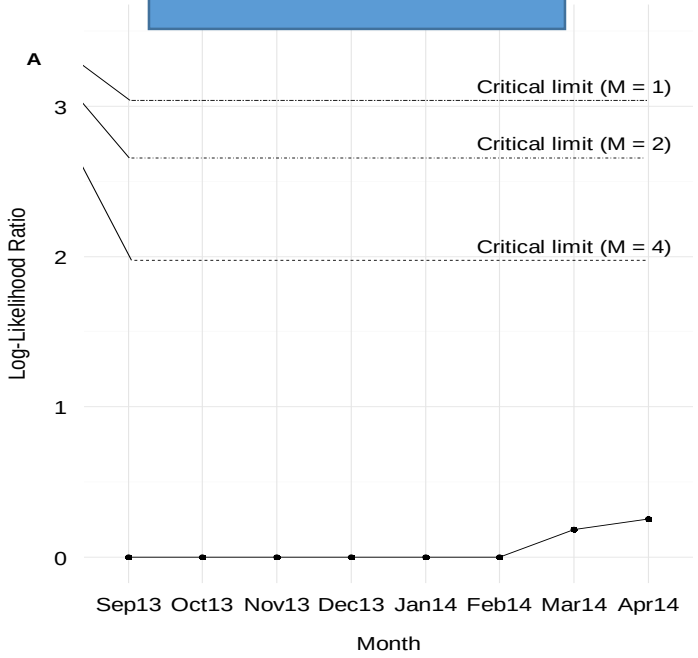
Trial implementation: results

Characteristic	Vaccine/outcome pair		
	Influenza/GBS Season 2013-14	Influenza/GBS Season 2014-15	MMR/Febrile seizures
Number of doses (n)	533,110	477,454	28,249
Sex – n (%)			
Male	240,884 (45.2)	216,224 (45.3)	14,474 (51.2)
Female	292,226 (54.8)	261,230 (54.7)	13,775 (48.8)
Age (years) – n (%)			
65-74	270,690 (50.8)	242,168 (50.7)	*
75-84	188,423 (35.3)	168,160 (35.2)	
≥85	73,997 (13.9)	67,126 (14.1)	
Age (months) – n (%)	*	*	
12			11,460 (40.6)
13			10,049 (35.6)
14			3,320 (11.8)
≥ 15			3,420 (12.1)

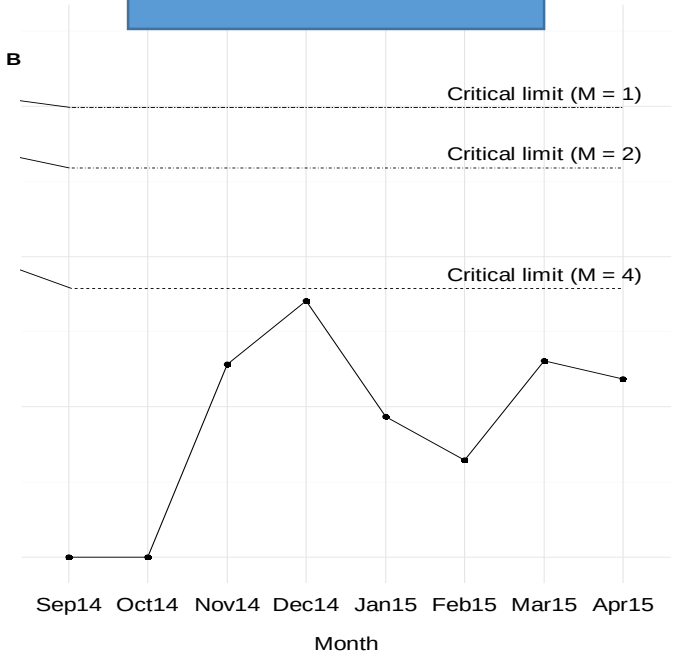
*Age (at time of vaccination) is expressed in years for seasonal influenza/GBS and months for MMR/febrile seizures.
GBS – Guillain-Barré syndrome, MMR – Measles-mumps-rubella.

Implementation: influenza vaccine/GBS

Season 2013-14



Season 2014-15



No signal detected in any of the seasons

Power and time to signal: influenza/GBS

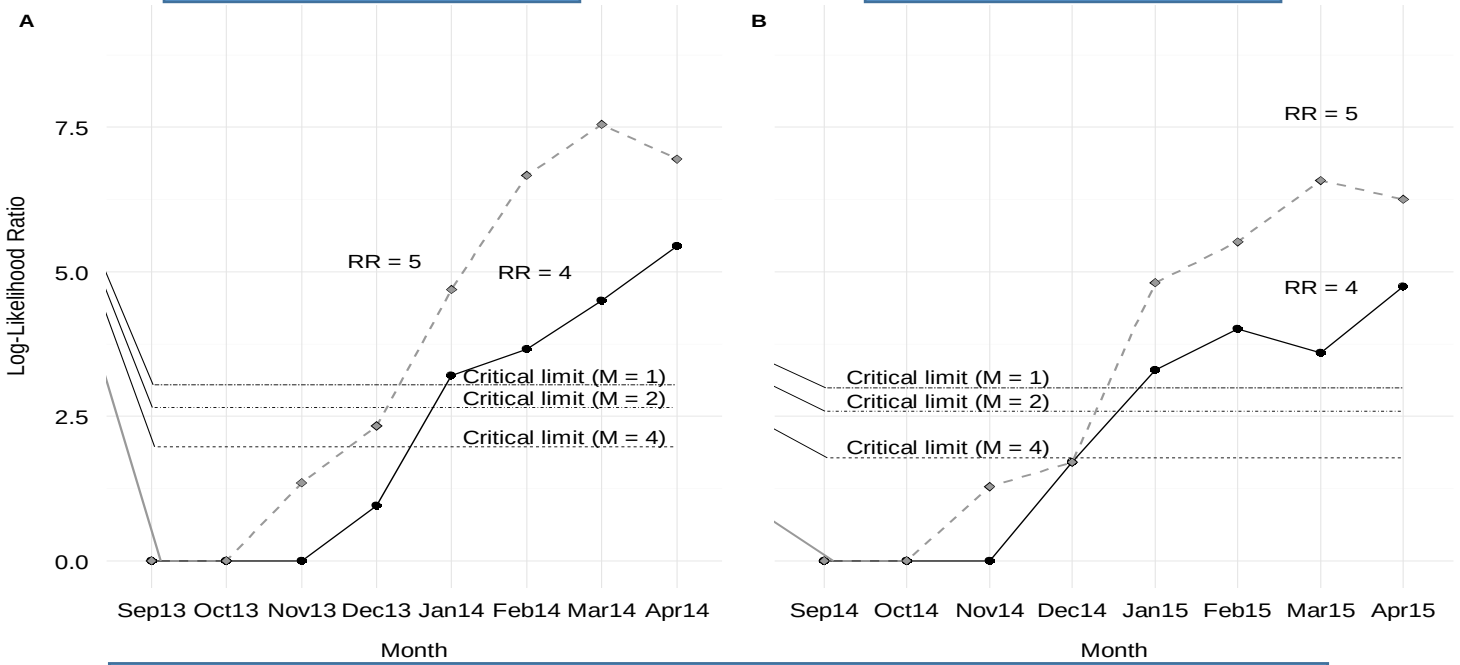
Minimum events	Season	Data available at	Power (time to signal in months from beginning of surveillance)*								
			Relative Risk								
			1.5	2	2.5	3	4	5	6	8	10
1	2013-14	07-04-2014	13	25	40	55 (4)	78 (4)	**91 (3)**	**97 (3)**	**100 (3)**	**100 (3)**
	2014-15	06-04-2015	12	23	37	51 (4)	74 (4)	**88 (4)**	**95 (4)**	**99 (3)**	**100 (3)**
2	2013-14	07-04-2014	14	28	44	60 (4)	**82 (4)**	**93 (3)**	**98 (3)**	**100 (3)**	**100 (3)**
	2014-15	06-04-2015	14	26	41	55 (4)	77 (4)	**90 (4)**	**96 (4)**	**100 (3)**	**100 (3)**
4	2013-14	07-04-2014	16	33	50	65 (4)	**86 (4)**	**95 (4)**	**98 (4)**	**100 (3)**	**100 (3)**
	2014-15	06-04-2015	16	31	47	62 (4)	**83 (4)**	**93 (4)**	**98 (4)**	**100 (4)**	**100 (4)**

Cells in bold refer to power ≥ 80%. * Time to signal is only displayed for cells where equivalent power ≥ 50%. PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio.

Implementation: influenza vaccine/GBS

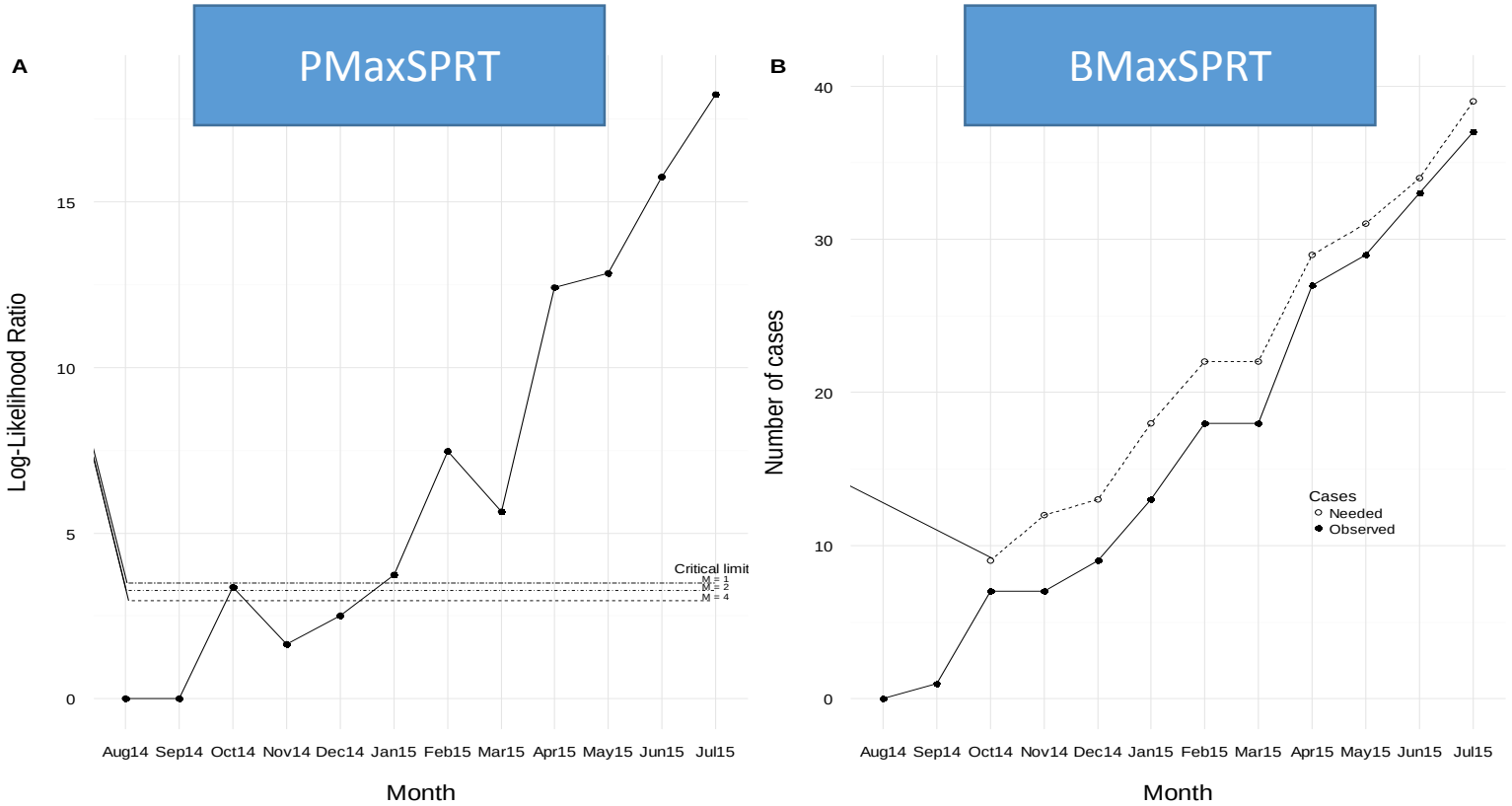
Season 2013-14

Season 2014-15



Signal detected assuming RR = 4/5

Implementation: MMR/seizures



Only for PMaxSPRT a signal is detected.

Power and time to signal: MMR/seizures

Minimum events	Season	Data available at	Power (time to signal in months from beginning of surveillance)*								
			Relative Risk								
			1.5	2	2.5	3	4	5	6	8	10
1	PMaxSPRT	06-07-2015	30	73 (5)	**95 (4)**	**99 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**
	BMaxSPRT	06-07-2015	28	63 (6)	**85 (6)**	**95 (5)**	**99 (5)**	**100 (4)**	**100 (3)**	**100 (3)**	**100 (3)**
2	PMaxSPRT	06-07-2015	33	76 (5)	**96 (4)**	**100 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**
4	PMaxSPRT	06-07-2015	36	79 (5)	**96 (4)**	**100 (3)**	**100 (2)**	**100 (1)**	**100 (1)**	**100 (1)**	**100 (1)**

Cells in bold refer to power ≥ 80%. * Time to signal is only displayed for cells where equivalent power ≥ 50%. BMaxSPRT - Binomial-based Maximized Sequential Probability Ratio, PMaxSPRT - Poisson-based Maximized Sequential Probability Ratio.

Trial implementation: summary

- For influenza/GBS we implemented a system in both seasons with no signal detected.
- Power to detect a signal was >80% for RR≥4. Implementation assuming RR=4/5 did signal;

- For MMR/seizures we were able to identify a signal with PMaxSPRT only.
- Power was >80% for RR≥2.5.

Conclusions

- NRTVSS is an option to quickly identify vaccine safety signals;
- Delays exist in CPRD but these are compatible with a near real-time system;
- CPRD can be used to implement NRTVSS, despite limited power to identify signals for a rare outcome.

Prospective Sequential Surveillance "Regulatory Perspective"

Efe Eworuke, PhD

Presented by: Sarah Dutcher, PhD

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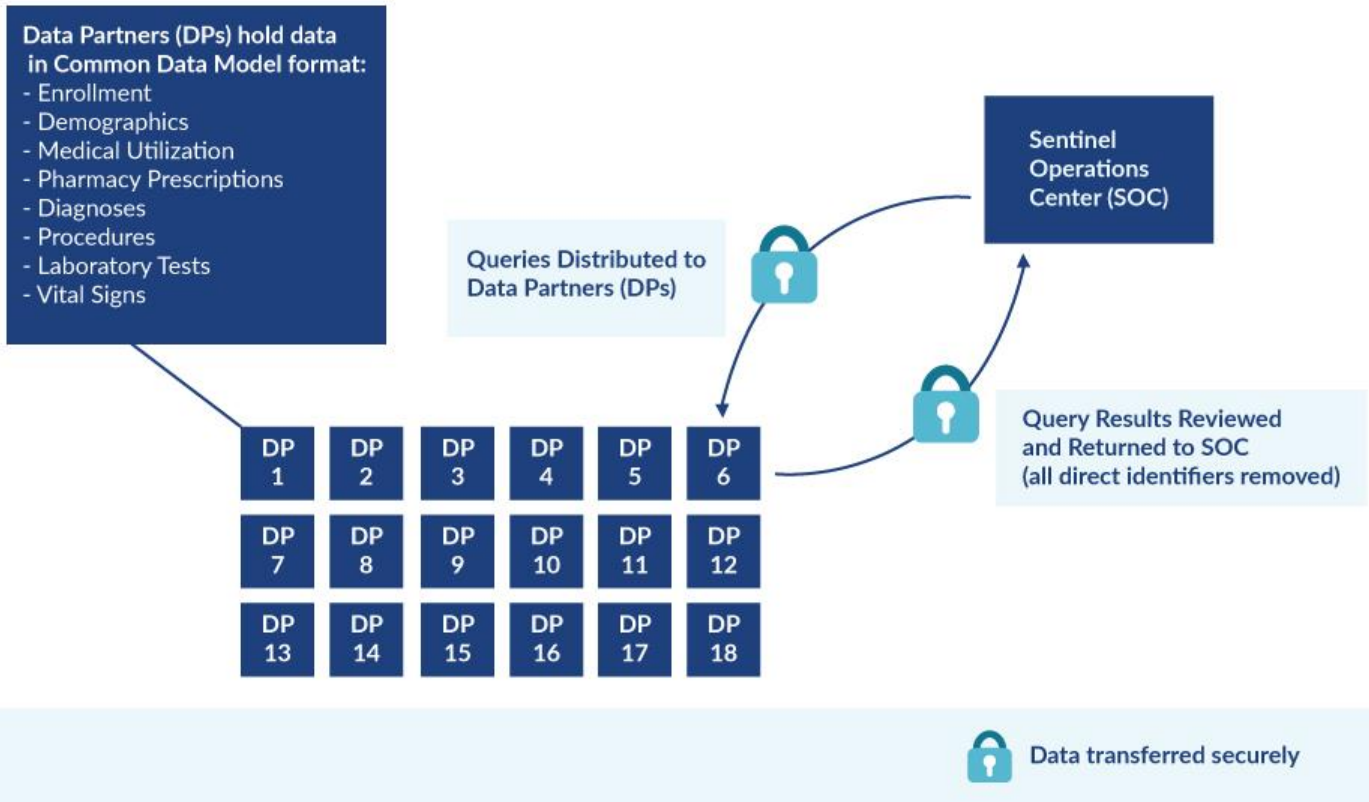
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclosures

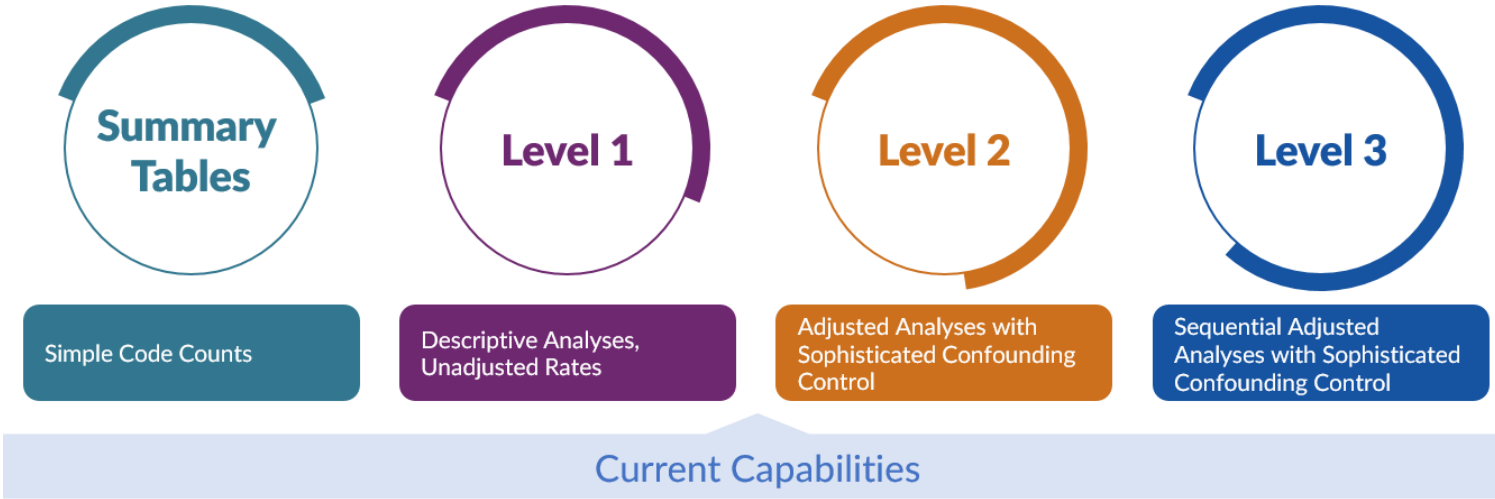
- The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the FDA
- No external funding to disclose

FDA's Sentinel System



Sequential Analysis in Sentinel

Prospective sequential analyses is one of Sentinel's Active Risk Identification and Analysis (ARIA) tools



Sequential Surveillance: Regulatory Context

- Formal study design
- Outcomes are checked using a plan that permits termination of surveillance with a determination that:
  - Additional investigation is needed
  - Results support a regulatory action
  - Any observed differences in safety fall within acceptable limits

Martin D, Gagne JJ, Gruber S, et al. Sequential surveillance for drug safety in a regulatory environment. *Pharmacoepidemiol Drug Saf*. 2018;27:707–712.

Why Prospective Sequential Surveillance?

- Characterize hypothesized risk not adequately powered in clinical trials
- Characterize observed risk in populations not adequately covered in clinical trials
  - Patients difficult to recruit (e.g., those with multiple comorbidities)
  - Minority populations
- Detect a potential undesirable exposure-outcome association earlier than a non-sequential analyses

Key Assumptions

Sequential boundaries and sequential test statistics are determined by assuming that:

1. Each new look includes all of the same data from prior looks (“anchoring” assumption)
2. Data are relatively stable and accurate, and therefore, worth anchoring on (“data stability” assumption)

Pilot Test Case in Sentinel

- Angiotensin-converting enzyme inhibitors (ACEI) and angioedema
  - Comparator: beta-blockers
  - Known positive exposure-outcome association
- Surveillance population and study criteria:
  - Claims-based databases in Sentinel
  - Age 18+ years with established new use of any study medication
  - Exclusion criteria: history of angioedema, use of ARB or aliskiren
  - Follow-up: treatment cessation, switch to another study or excluded drug, disenrollment, outcome, death, 60 days, end of study period
- Outcomes monitored:
  - Angioedema (ICD-9: 995.1, ICD-10: T783XXA)
  - Serious angioedema (presence of angioedema diagnosis + inpatient care management)

Implementation Challenges in Postmarketing Settings

- Dynamic Data Environment
  - Investigators have to allow time for corrections to claims data
  - Data lag often differs between Data Partners in a distributed database setting
  - Data lag may complicate prospective sequential surveillance
- Variable outcome risk windows
  - Risk may not be fixed at a single data look
  - Challenge when risk window is variable and spans across data refreshes

Implementation Challenges in Postmarketing Settings

Three surveillance modes to meet anchoring assumptions:

- **Full lock**
  - Requires data to be strictly incremental: matched pair cannot be broken across looks
  - Already-analyzed information cannot be updated in subsequent looks
  - Limitation: Potential misclassification if data is incomplete during an interim analyses
- **Partial lock**
  - Data is added incrementally
  - Allows data for an interim look to be updated if new information comes in from subsequent look
  - Limitation: Incomplete information in prior looks if subsequent look adds information, which can affect test statistic for inferences
- **Re-matching / No lock**
  - Re-do PS estimation and PS matching at each look
  - Uses the most updated information
  - Limitation: Anchoring assumption is not met

Implementation Challenges in Postmarketing Settings

- Multiple outcomes under surveillance
  - Setting the same end of surveillance may be challenging if outcomes under consideration do not occur at the same rate
  - How long do we continue to monitor for each outcome?
    - Use of maximum length of surveillance
    - Follow-up descriptively
- Uptake of product
  - Changes in practice recommendations, guidelines
  - Formulary changes

Implementation Challenges in Postmarketing Settings

- Expected time to signal is an important criterion in postmarketing surveillance
  - Unlike clinical trials, it is often more desirable to detect a signal early (if any) in the post-approval setting
  - Determined by parameter selection
- Trade-off between looking as the data arrive (continuous sequential) vs. looking at intervals (group sequential)

Parameter Considerations for Sequential Analysis

- **Maximum length of surveillance**: Number of outcomes needed to stop surveillance, when the null is not rejected
- **Total type I error:** 0.05
- **Shape of the alpha spending function:** rho can be set at 0.5, 1, or 2
  - To “spend” more alpha in earlier looks, balanced over time, or in later looks
- **Minimum number of events:** Number of outcomes required to begin hypothesis testing

Test Case Parameter Selection

- Surveillance mode: Partial lock
- Propensity score adjustment: Compared stratification and matching
- Assumed mean probability of being exposed: 0.56
- Maximum length of surveillance:
  - Angioedema: 112
  - Serious angioedema: 25
- Total type I error: 0.05
- Shape of the alpha spending function: rho = 0.5
- Minimum number of outcomes: 5

Test Case Results: Angioedema

Exposure Definition	Monitoring Period	New Users	Person Years at Risk	Average Person Days at Risk	Number of Events	Hazard Ratio (95% CI)
Unmatched Analysis (Site-adjusted only)						
ACE Inhibitors	1	498,360	67,665.43	49.59	530	2.90 (2.40, 3.52)
Beta Blockers		381,633	47,898.43	45.84	132	
ACE Inhibitors	2	620,604	85,792.13	50.49	674	2.96 (2.50, 3.51)
Beta Blockers		479,025	61,196.84	46.66	166	
1:1 Matched Unconditional Analysis; Caliper=0.025						
ACE Inhibitors	1	288,908	38,989.41	49.29	349	3.17 (2.54, 3.94)
Beta Blockers		288,908	36,195.30	45.76	104	
ACE Inhibitors	2	362,038	49,777.84	50.22	444	3.35 (2.75, 4.09)
Beta Blockers		362,038	46,201.77	46.61	125	
Predefined Deciles Analysis						
ACE Inhibitors	1	498,360	67,665.43	49.59	530	3.41 (2.79, 4.17)
Beta Blockers		381,633	47,898.43	45.84	132	
ACE Inhibitors	2	620,604	85,792.13	50.49	674	3.59 (3.00, 4.30)
Beta Blockers		479,025	61,196.84	46.66	166	

Discussion/Lessons Learned

- Selection of parameters depends on the regulatory question
  - Weigh relative importance of stopping boundaries: expected time to signal vs. maximum length of surveillance
- There are unique challenges when conducting sequential surveillance in observational data
  - Data timeliness depends on the source data
    - Sentinel is based on secondary use of administrative claims
  - Data stability is impacted by claims adjustments, number of contributing sources (Data Partners), refresh rate

Acknowledgements

Many thanks are due to the Sentinel Data Partners who provided data used in the pilot study


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Sequential Surveillance Demonstration and Exercise

Judith C. Maro

https://www.sequentialanalysis.org

Search

R Sequential Analysis

Exact Sequential Analysis for Poisson and Binomial Data

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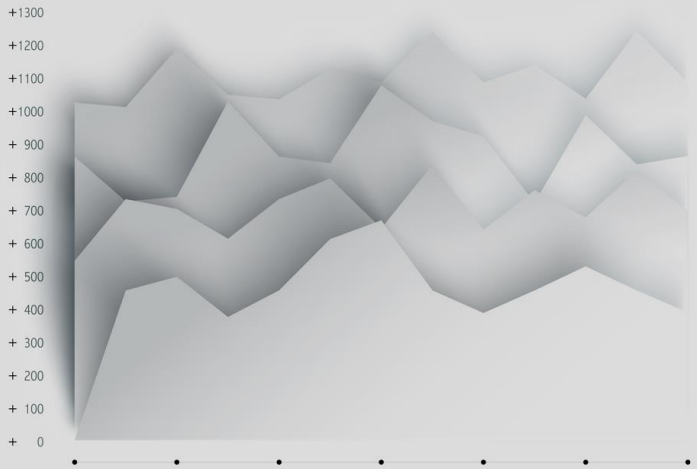

www.sequentialanalysis.org

Home

This is a web-based interface for the R Sequential package, with which you can conduct exact sequential analyses for binomial and Poisson data. It allows you to run the R Sequential package online, without installing and managing an R programming environment, and without writing any code in the R programming language. Functions to calculate statistical power, expected time to signal and required sample sizes for performing exact sequential analysis are also provided. All these calculations can be done for either Poisson or binomial data, and for different types of rejection boundaries. In the case of group sequential analyses, the group sizes do not have to be specified in advance.

For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from **R Sequential version 2.3.2**.

R Sequential Features

1. **Signaling threshold functions** – the *CV* and *Threshold* suite – that help investigators develop optimal statistical stopping boundaries.
2. **Planning functions** – the *Performance* and *SampleSize* suite – that develop statistical power information before you select your parameters for surveillance.
3. **Implementation functions** – the *Analyze* suite – that execute sequential analysis according to the chosen study design.

Performing Sequential Statistical Analysis

- You are performing a study to monitor Outcome Y following new Drug A v. Drug B use with a 1:1 propensity-score matched design.
- You intend to monitor outcomes sequentially.
- For simplicity, in this example, we will assume the matching ratio or probability of exposure is **fixed** – so if one part of a matched pair censors (i.e., disenrolls, dies, has outcome), the other part of the pair censors too.
- **Recall:** We have two statistical stopping boundaries: 1) the rejection of the null hypothesis in case of a detected elevated hazard ratio and 2) the failure to reject the null hypothesis by the end-of-study.

Tradeoff between Two Stopping Boundaries

Sentinel

Sequential Information Time to detect a Twofold Relative Risk with 90% Statistical Power and Overall Type 1 Error=0.05 (one-sided).

	Continuous	4 Hypothesis Tests	2 Hypothesis Tests	Non-Sequential
Maximum Sample Size (in **Total** Events)	112	92	84	78
Mean Time-to-Signal (in **Total** Events)	44.2	50.4	57.5	78

https://www.sequentialanalysis.org

Search

R Sequential Analysis

Exact Sequential Analysis for Poisson and Binomial Data

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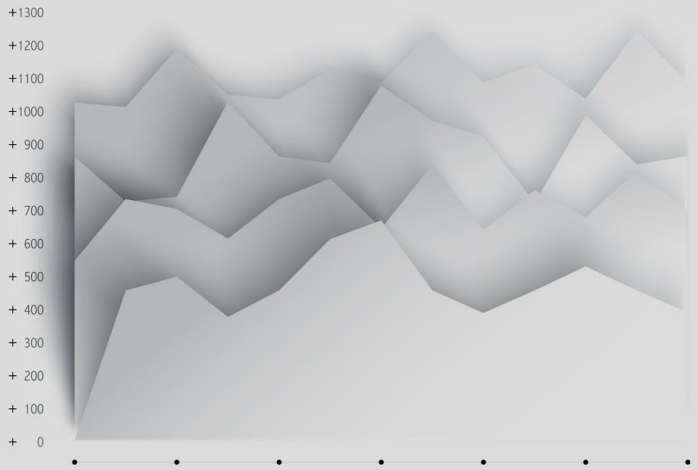

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For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from **R Sequential version 2.3.2**.

Browse as Guest and Proceed to Sequential Analysis

Sentinel

Home

You are now browsing as a Guest User. You may interact with the site, but your work will be deleted at the end of the browsing session. To save your work, please convert this temporary Guest account to a permanent User account with the "Convert Guest Account..." button. Clicking the "End Guest Session" button will log you out without saving your work.

Convert Guest Account ➜ User Account | End Guest Session (Work will not be saved!)

This is a web-based interface for the R Sequential package, with which you can conduct exact sequential analyses for binomial and Poisson data. It allows you to run the R Sequential package online, without installing and managing an R programming environment, and without writing any code in the R programming language. Functions to calculate statistical power, expected time to signal and required sample sizes for performing exact sequential analysis are also provided. All these calculations can be done for either Poisson or binomial data, and for different types of rejection boundaries. In the case of group sequential analyses, the group sizes do not have to be specified in advance.

For complete documentation, please read the R Sequential User Guide and the scientific papers in the reference list.

This site is currently using selected functions from **R Sequential version 2.3.2**.

Proceed to Sequential Analysis

Set-up the Binomial Analysis

Sentinel

Home / Analysis Index

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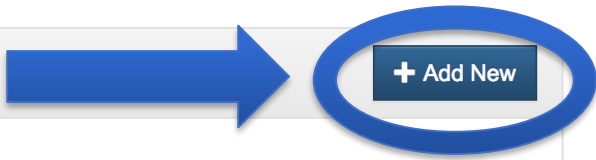
Convert Guest Account ➜ User Account | End Guest Session (Work will not be saved!)

Sequential Analysis

Analyze.Binomial



You have no Analyze.Binomial analyses.

Enter Surveillance Parameters

- N= 100 (Maximum Length of Surveillance in **Total** Events)
- alpha= 0.05 (Total one-sided Type 1 error)
- AlphaSpendType = Wald (Shape)
- zp=1 (Matching Ratio)
- M=5 (Minimum Number of Events to Perform Tests)
- Title = Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

Enter Setup Parameters For A New Analyze.Binomial Analysis

name

My New Analysis

Name of the analysis.

N

100

Maximum sample size, at which the sequential analysis stops without rejecting the null hypothesis. No default value. (This site allows a maximum value of N=1000.)

alpha

0.05

Overall significance level. Must be in the range (0,0.5]. Default is alpha=0.05.

AlphaSpendType

Wald

The type of alpha spending function to be used. With the Wald option, the Wald type upper rejection boundary is used, which is flat with respect to the likelihood ratio. With the power-type option, the alpha spending uses a power function with parameter rho, with rho defined by the user. This alpha spending setting is automatically used when the Analyze.Binomial function is run, but during the sequential analysis, and before each test, the user can always specify an arbitrary amount of alpha spending to be used up until and including that test.

zp

1

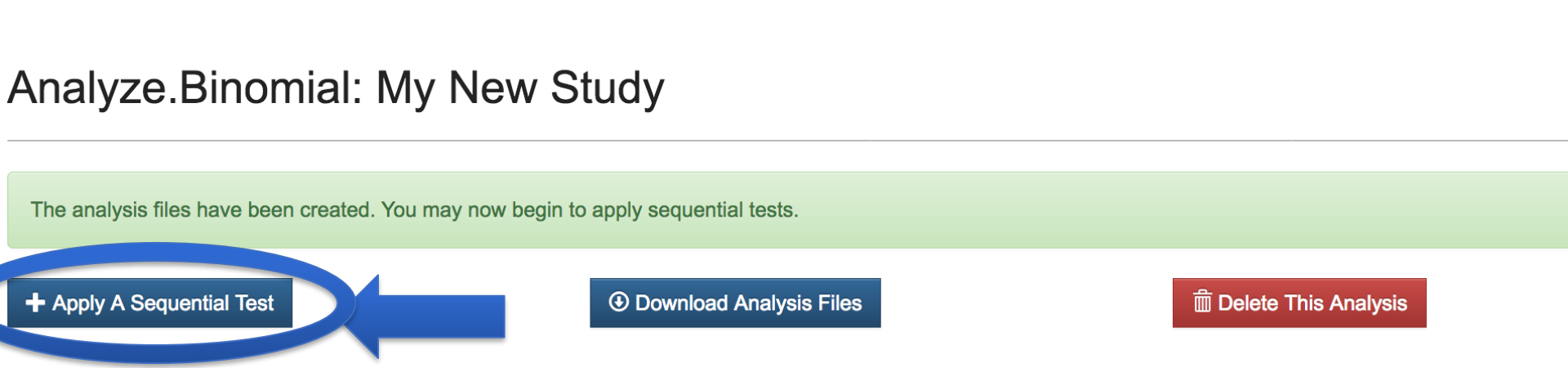
The prediction for z, the expected ratio between cases and controls under the null hypothesis that will be specified in the Analyze.Binomial function. This variable is only used when Alphaspendtype='Wald', and it is used to calculate the appropriate rejection boundary. If the z used in Analyze.Binomial during the actual sequential analysis is different from zp, that is okay, and the sequential analysis will still maintain the correct alpha level. Default is z=1.

M

5

Minimum number of events required before the null hypothesis can be rejected. Must be a positive integer. Default is m=1.

Set-Up is Complete! Now, Time for the Analysis



Add Sequential Hypothesis Test #1

Test No.	Z (Ratio)	Cases**	Controls**
Test 1	1	2	2

Knowledge Check: Who knows what's going to happen?

**The software refers to "cases" as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to "controls" as the number of outcome events that occurs in the comparator or referent group of interest.

Analyze.Binomial: My New Analysis - Add Test (#1)

z

1

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a selfcontrol analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

2

A number or a vector of the same length as z containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

controls

2

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probabiliy) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

+ Add Test

Results after Hypothesis Test #1

Sentinel

Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

=> H0 cannot be rejected yet because the cumulative events is still smaller than M.

			Cumulative					--alpha spent--			
Test	Cases	Controls	Cases	Controls	E[Cases|H0]	RR estimate	LLR	target	actual	CV	Reject H0
1	2	2	2	2	2.00	1.00	0.000000	0	0	<NA>	No

Parameter settings: N= 100, alpha= 0.05, rho= n, Tailed= 1, and M= 5, H0: RR<= 1.
Analysis performed on Tue Aug 21 10:48:58 2018.

+ Apply Another Sequential Test

Download Analysis Files

Delete This Analysis

Add Sequential Hypothesis Test #2

Test No.	Z (Ratio)	Cases	Controls
Test 1	1	2	2
Test 2	1	21	10

**The software refers to “cases” as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to “controls” as the number of outcome events that occurs in the comparator or referent group of interest.

Analyze.Binomial: My New Analysis - Add Test (#2)

z

1

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a selfcontrol analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

21

A number or a vector of the same length as z containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

controls

10

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probabiliy) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

+ Add Test

Results after Hypothesis Test #2

Sentinel

Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

=> Do not reject H0. Proceed to a new test as soon as you have more data.

			----- Cumulative	--------			--alpha spent--			
Test	Cases	Controls	Cases	Controls	E[Cases|H0]	RR estimate	LLR	target	actual	CV	Reject H0
1	2	2	2	2	2.00	1.00	0.000000	0.0000	0.0000	<NA>	No
2	21	10	23	12	17.50	1.92	1.758216	0.0343	0.0205	24	No

Parameter settings: N= 100, alpha= 0.05, rho= n,zp= 1, and M= 5, H0: RR<= 1.

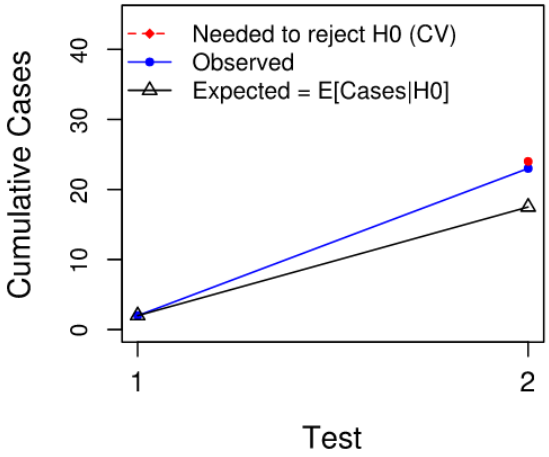
Analysis performed on Tue Aug 21 10:54:32 2018.

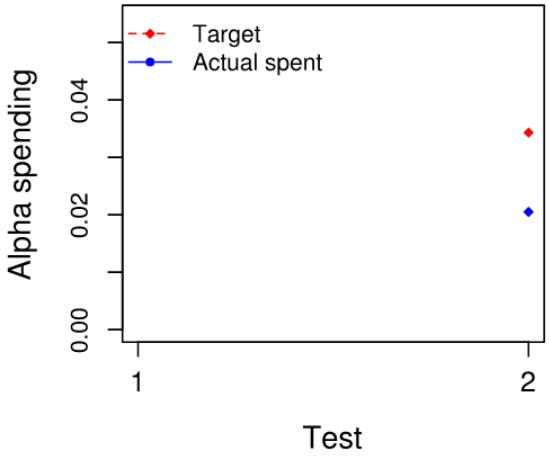
+ Apply Another Sequential Test

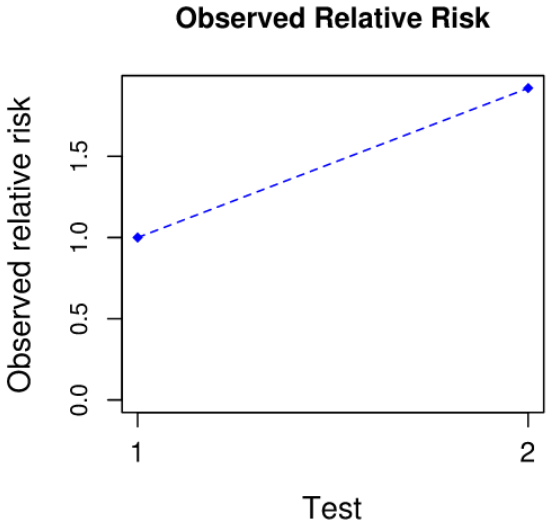
Download Analysis Files

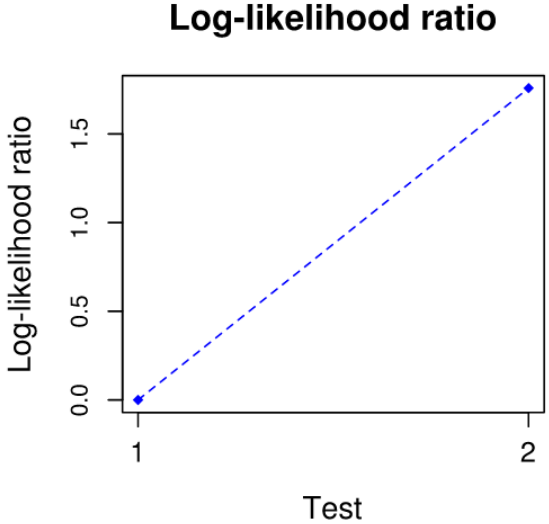
Delete This Analysis

Additional Graphical Output after Test #2









Add Sequential Hypothesis Test #3

Test No.	Z (Ratio)	Cases	Controls
Test 1	1	2	2
Test 2	1	21	10
Test 3	1	16	9

**The software refers to “cases” as the number of outcome events that occurs in the exposed or treatment group of interest. The software refers to “controls” as the number of outcome events that occurs in the comparator or referent group of interest.

Analyze.Binomial: My New Analysis - Add Test (#3)

z

1

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a selfcontrol analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

16

A number or a vector of the same length as z containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

controls

9

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probabiliy) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

+ Add Test

Results after Hypothesis Test #3

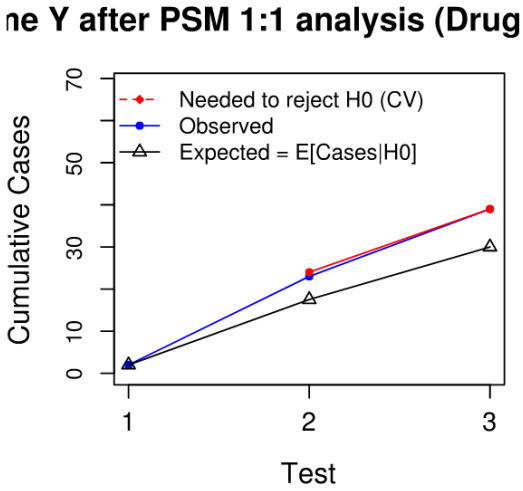
Outcome Y after PSM 1:1 analysis (Drug A v. Drug B)

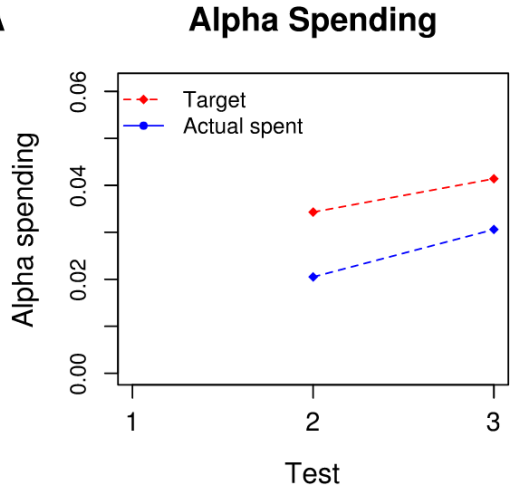
=> Reject H0. No further sequential analyses are needed.

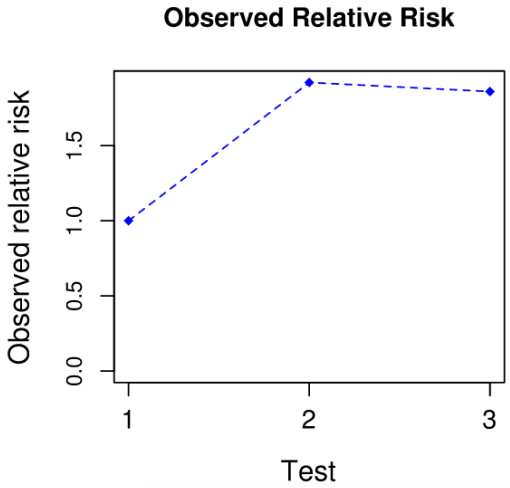
Test	Cases	Controls	Cumulative Cases	Cumulative Controls	E[Cases|H0]	RR estimate	LLR	--alpha spent-- target	--alpha spent-- actual	CV	Reject H0
1	2	2	2	2	2.00	1.00	0.000000	0.0000	0.0000	<NA>	No
2	21	10	23	12	17.50	1.92	1.758216	0.0343	0.0205	24	No
3	16	9	39	21	30.00	1.86	2.742032	0.0414	0.0306	39	Yes

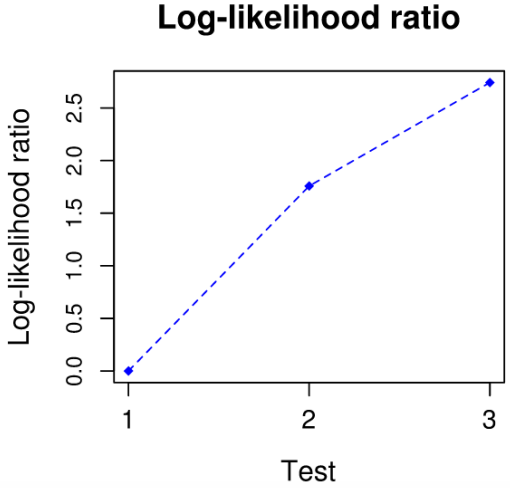
Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 18:29:00 2018.

Additional Graphical Output after Test #3









Add a Non-Sequential Version of My New Analysis

Sentinel

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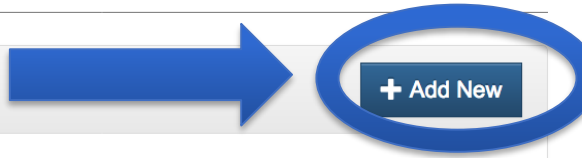
Convert Guest Account ➜ User Account | End Guest Session (Work will not be saved!)

Sequential Analysis

Analyze.Binomial



Name	Number of Tests	Created	Last Updated	R Sequential Version
My New Analysis	4	Aug. 21, 2018	Aug. 21, 2018	2.3.2

Enter Setup Parameters For A New Analyze.Binomial Analysis

name

Non-Sequential Version of My New Analysis

Name of the analysis.

N

100

Maximum sample size, at which the sequential analysis stops without rejecting the null hypothesis. No default value. (This site allows a maximum value of N=1000.)

alpha

0.05

Overall significance level. Must be in the range (0,0.5]. Default is alpha=0.05.

AlphaSpendType

Wald

The type of alpha spending function to be used. With the Wald option, the Wald type upper rejection boundary is used, which is flat with respect to the likelihood ratio. With the power-type option, the alpha spending uses a power function with parameter rho, with rho defined by the user. This alpha spending setting is automatically used when the Analyze.Binomial function is run, but during the sequential analysis, and before each test, the user can always specify an arbitrary amount of alpha spending to be used up until and including that test.

zp

1

The prediction for z, the expected ratio between cases and controls under the null hypothesis that will be specified in the Analyze.Binomial function. This variable is only used when Alphaspendtype='Wald', and it is used to calculate the appropriate rejection boundary. If the z used in Analyze.Binomial during the actual sequential analysis is different from zp, that is okay, and the sequential analysis will still maintain the correct alpha level. Default is z=1.

M

5

Minimum number of events required before the null hypothesis can be rejected. Must be a positive integer. Default is m=1.

title

Non-Sequential PSM 1:1 Outcome Y

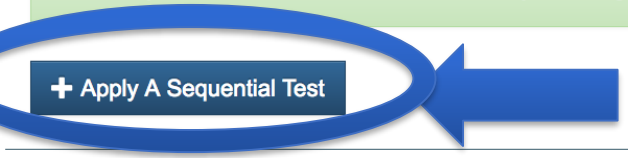
Title for the results shown in the output tables and the illustrative graphics. Can be any text string. Default is no title.

Same Surveillance Parameters as BEFORE

- N= 100 (Maximum Length of Surveillance)
- alpha= 0.05 (Total Type 1 error)
- AlphaSpendType = Wald (Shape)
- zp=1 (Matching Ratio)
- M=5 (Minimum Number of Events to Perform Tests)
- Title = Non-Sequential PSM 1:1 Outcome Y

Analyze.Binomial: Non-Sequential Version of My New Analysis

The analysis files have been created. You may now begin to apply sequential tests.



Download Analysis Files

Delete This Analysis

Add Non-Sequential Hypothesis Test #1

Test No.	Z (Ratio)	Cases	Controls
Test 1	1	2	2
Test 2	1	21	10
Test 3	1	16	9
Test 4	1	28	12
Non-Sequential	1	67	33

Analyze.Binomial: My Non-Sequential Analysis - Add Test (#1)

z

1

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a selfcontrol analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

67

A number or a vector of the same length as z containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

controls

33

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

no override

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probabiliy) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

+ Add Test

Analyze.Binomial: My Non-Sequential Analysis

Sentinel

```
                              Non-Sequential PSM 1:1 for Outcome Y
--------------------------------------------------------------------------------------------
=>    Reject H0. No further sequential analyses are needed.
--------------------------------------------------------------------------------------------
                      ----- Cumulative    --------                        --alpha spent--
 Test Cases Controls Cases   Controls E[Cases|H0] RR estimate      LLR  target  actual CV Reject H0
    1    67       33    67         33       50.00        2.03 5.896854  0.0500  0.0443 59       Yes
============================================================================================
Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 18:38:34 2018.
============================================================================================
```

Compare with the sequential test version below. Note the difference in the information time required to signal (100 total outcomes v. 60 total outcomes).

```
    3    16        9    39         21       30.00        1.86 2.742032  0.0414  0.0306   39       Yes
```

Knowledge Check

- We looked at a 3-test sequence that reached a stopping boundary with 60 total outcomes accumulated (39/21 split with p=0.5 / z=1)
- What if our first bolus of data had those 60 outcomes with the same split?
  - Would you reach the stopping boundary?
  - Will the number of treatment group outcomes needed to reach the stopping boundary be a) higher? b) lower? or c) the same?

```
-------------------------------------------------------------------------------------------
=>    Reject H0. No further sequential analyses are needed.
-------------------------------------------------------------------------------------------
                      ----- Cumulative    --------                        --alpha spent--
 Test Cases Controls Cases   Controls E[Cases|H0] RR estimate      LLR  target  actual CV Reject H0
    1    39       21    39         21       30.00        1.86 2.742032  0.0414  0.0259 38       Yes
===========================================================================================
Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 19:01:09 2018.
===========================================================================================
```

Compare with the sequential test version below

```
    3    16        9    39         21       30.00        1.86 2.742032  0.0414  0.0306   39       Yes
```

What if you need an answer NOW?

- Let's rewind and go back to Test #1 in our sequential analysis when we still had not signaled.
- Despite the best-laid plans, low uptake means that you will not be able to monitor Outcome Y for the rest of the planned surveillance – you will need to terminate surveillance at Test 2. What do you do?

Test No.	Z (Ratio)	Cases	Controls
Test 1	1	2	2
Test 2	1	21	10

Analyze.Binomial: My New Analysis - Finished Early - Add Test (#2)

z

1

For a matched case-control analysis, z is the number of controls matched to each case. For example, if there are 3 controls matched to each case, z=3. In a selfcontrol analysis, z is the ratio of the length of the control interval to the length of the risk interval. For example, if the risk interval is 2 days long and the control interval is 7 days long, z=7/2. In terms of p, the binomial probability under the null hypothesis, p=1/(1+z), or equivalently, z=1/p-1. The parameter z must be a positive number. The default value is z=1 (p=0.5). If the ratio is the same for all observations, then z can be any positive number. If the ratio is different for different observations, then z is a vector of positive numbers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

cases

21

A number or a vector of the same length as z containing the number of cases.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

controls

10

A number or a vector of the same length as z containing the number of controls.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

AlphaSpend

0.05

The alpha spending function is specified in the AnalyzeSetUp.Binomial function. At any look at the data, it is possible to over ride that pre-specified alpha spending plan by using the AlphaSpend parameter. AlphaSpend is a number representing the maximum amount of alpha (Type I error probabiliy) to be spent up to and including the current test. Because of the discrete nature of the binomial distribution, the actual amount of alpha spent may be less than the maximum amount specified. It must be in the range (0,alpha]. The default value is no override, which means that the function will use the alpha spending plan specified in the AnalyzeSetUp.Binomial function.

+ Add Test

Test Results after Alpha Override to Force-Quit Surveillance

Sentinel

Analyze.Binomial: My New Analysis - Finished Early

```
                                Early Finish
-------------------------------------------------------------------------------------------
=>    Reject H0. No further sequential analyses are needed.
-------------------------------------------------------------------------------------------
                     ----- Cumulative    --------                      --alpha spent--
 Test Cases Controls Cases   Controls E[Cases|H0] RR estimate      LLR  target  actual   CV Reject H0
    1     2        2     2          2        2.00        1.00 0.000000  0.0000  0.0000 <NA>        No
    2    21       10    23         12       17.50        1.92 1.758216  0.0500  0.0448   23       Yes
===========================================================================================
Parameter settings: N= 100, alpha= 0.05, rho= n, zp= 1, and M= 5, H0: RR<= 1.
Analysis performed on Thu Aug 23 18:46:19 2018.
===========================================================================================
```

Important Takehomes

- Hitting an early stopping boundary means that you identified a potential elevated risk worthy of additional scrutiny.
  - It occurs prior to the total sample size you had planned (consider 60 outcomes instead of 100 outcomes) – there is less information there (and hence, more uncertainty in the risk estimate).
- You don't have to stop monitoring. You can continue to collect data on the outcome, verify the existing data, and/or perform additional investigations.
- You do have to stop performing sequential hypothesis tests in the current analysis, but you can continue to develop risk estimate information.

Other R Sequential Analysis or R Functions

- Poisson Analysis is also available
  - As Andreia discussed, Poisson functions compare observed outcomes to expected outcomes where expected outcomes are given by a flat rate that increments as follow-up time among the observed group accrues.

- More Complex Functions are available in R: https://cran.r-project.org/web/packages/Sequential/index.html
  - Includes Conditional Poisson Analysis.
  - Includes a more sophisticated suite of equations to find optimal alpha spending plans.

Recall Case-Centered Logistic Regression Paper

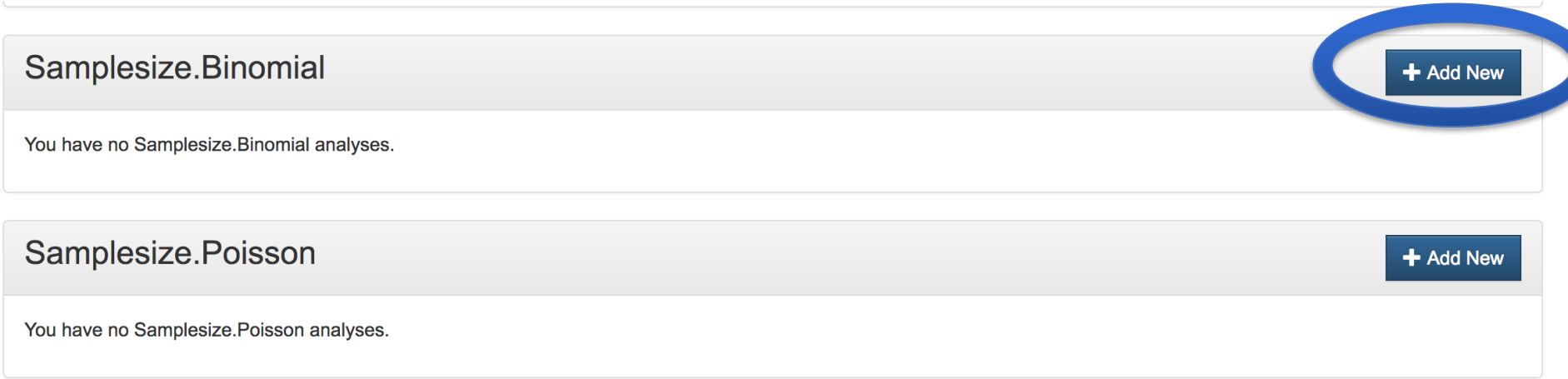
- It is possible for Z to be a summation over multiple risk sets (e.g., different matching ratios, different amounts of contributed time)
- EXAMPLE:

Test No.	Z (Ratio)	Cases	Controls
Test 1	(1,2)	(2,0)	(1,1)
Test 2	(1,2)	(19,2)	(7,3)

R Sequential Features

1. **Signaling threshold functions** – the *CV* and *Threshold* suite – that help investigators develop optimal stopping boundaries.
2. **Planning functions** – the *Performance* and *SampleSize* suite – that develop statistical power information before you select your parameters for surveillance.
3. **Implementation functions** – the *Analyze* suite – that execute sequential analysis according to the chosen study design.

Calculate Sample Size for Binomial Data



Enter Several Relative Risks and Powers

- RR= 1.5,2,3
- alpha= 0.05
- Power = 0.90,0.85,0.80
- M=5
- z=1

Enter Parameters For A New Samplesize.Binomial Analysis

name

My New Analysis

Name of the analysis.

RR

1.5,2,3

A target vector of relative risks to be detected with the requested statistical powers.

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

alpha

0.05

The significance level. The default value is "alpha=0.05". Must be in the range (0, 0.5].

power

0.90,0.85,0.80

The target vector of overall statistical powers to detect an increased risk of the relative risk (RR). The default value is "power=0.90".

Enter vector data as a comma-separated list of values - e.g. '1,2,3'. Do not add spaces or any other characters. Do not wrap vector data with 'c()' as if you were using the R functions directly; the system does that for you.

M

5

The minimum number of events needed before the null hypothesis can be rejected. It must be a positive integer. The default value is "M=1".

z

1

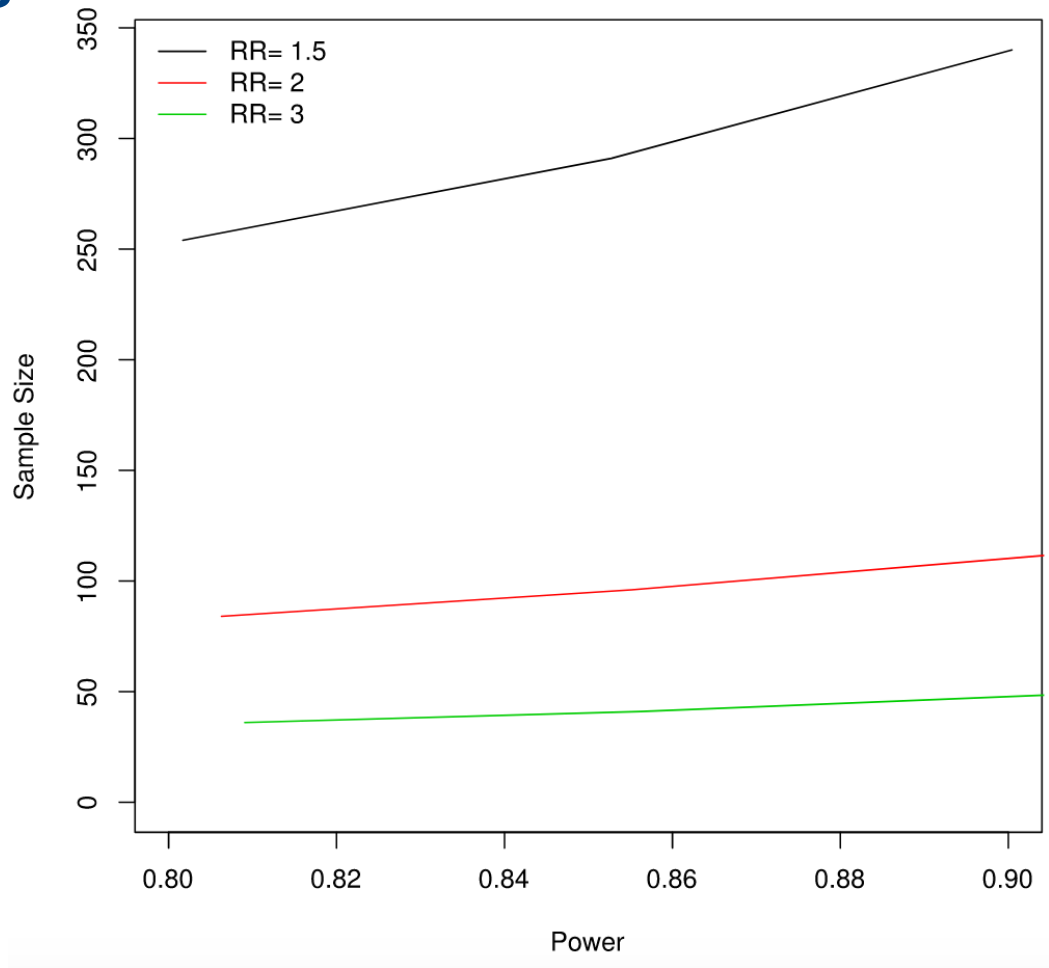
For a matched case-control analysis, z is the number of controls matched to each case under the null hypothesis. There is no default value.

While that's running…

Samplesize.Binomial: My New Analysis

	Target RR	Target power	Sample Size	Critical value	Type I Error prob.	Actual power
[1,]	1.5	0.80	254	3.75651	0.04998989	0.8016928
[2,]	1.5	0.85	291	3.80962	0.04995446	0.8527304
[3,]	1.5	0.90	340	3.85490	0.04998340	0.9004340
[4,]	2.0	0.80	84	3.46574	0.04617813	0.8062950
[5,]	2.0	0.85	96	[illegible]	0.04779212	0.8551184
[6,]	2.0	0.90	112	[illegible]	0.04946143	0.9057856
[7,]	3.0	0.80	36	3.42972	0.04880955	0.8090669
[8,]	3.0	0.85	41	[illegible]	0.03705363	0.8562287
[9,]	3.0	0.90	49	[illegible]	0.03880460	0.9084408

While that's running…



Summary and Audience Questions

- Today, we wanted to talk about:
  - Sequential Statistical Theory
  - Applied Uses in Research and Regulatory Settings
  - How to do an analysis, thereby developing intuition with it

- Audience Questions